REMARKS

Reconsideration and allowance are respectfully requested.

Claims 28-30, 32, 34-42, 44, 46-56, 58-67 and 71-72 are pending.

The amendments are fully supported by the original disclosure and, thus, no new matter is added by their entry. Support for the claim amendments may be found, inter alia, at page 10, line 25, and page 11, line 3, of the specification.

35 U.S.C. 103 – Nonobviousness

To establish a case of prima facie obviousness, all of the claim limitations must be taught or suggested by the prior art. See M.P.E.P. § 2143.03. Obviousness can only be established by combining or modifying the prior art teachings to produce the claimed invention if there is some teaching, suggestion, or motivation to do so found in either the references themselves or in the knowledge generally available to a person of ordinary skill in the art. See, e.g., *In re Fine*, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988); *In re Jones*, 21 USPQ2d 1941, 1943-44 (Fed. Cir. 1992). It is well established that the mere fact that references can be combined does not render the resultant combination obvious unless the desirability of that combination is also taught or suggested by the prior art. See *In re Mills*, 16 USPQ2d 1430, 1432 (Fed. Cir. 1990). Thus, even if all elements of the claimed invention were known, this is not sufficient by itself to establish a prima facie case of obviousness without some evidence that one would have been motivated to combine those teachings in the manner proposed by the Examiner. See *Ex parte Levengood*, 28 USPQ2d 1300, 1302 (B.P.A.I. 1993).

Evidence of the teaching, suggestion or motivation to combine or to modify references may come explicitly from statements in the prior art, the knowledge of a person of ordinary skill in the art or the nature of the problem to be solved, or may be implicit from the prior art as a whole rather than expressly stated in a reference. See *In re Dembiczak*, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999); *In re Kotzab*, 55 USPQ2d 1313, 1316-17 (Fed. Cir. 2000). Rigorous application of this requirement is the best defense against the subtle, but powerful, attraction of an obviousness analysis based on hindsight. See *Dembiczak* at 1617. Whether shown explicitly or implicitly, however,

broad conclusory statements standing alone are not evidence because the showing must be clear and particular. See *id.*

Finally, a determination of *prima facie* obviousness requires a reasonable expectation of success. See *In re Rinehart*, 189 USPQ 143, 148 (C.C.P.A. 1976).

Claims 28-30, 32, 34-42, 44, 46-56, 58-67 and 71-72 were rejected under Section 103(a) as allegedly unpatentable over Fondy et al. (EP 0297946) in view of Richman et al. (J. Biol. Res. Mod. 9:570-575, 1990) taken together with Lane et al. (WO 94/12202) and further in view of Muggia et al. (*Avery's Drug Treatment*, 1987). Applicants traverse.

It was alleged at page 3 of the Action, "Fondy et al. teach a method of treating cells in vivo and in vitro comprising a protective cytochalasin compound . . . and an antineoplastic agent such as the vinca alkaloids . . . wherein the components can be administered sequentially" (citations omitted). But this is an incorrect interpretation of Fondy et al. Instead, the cited reference discloses the use of cytochalasins alone, as an antineoplastic drug by itself. This is evident from the first two lines of page 2, and the paragraph at page 3, lines 48-55. Cytochalasin is used by Fondy et al. as a chemotherapeutic agent because of its intrinsic antineoplastic activity, or in a combination therapy with another chemotherapeutic agent to obtain an additive effect. There is no teaching or suggestion of cytochalasin as a protective compound.

It was also alleged at page 3 of the Action, "Fondy et al. state that the cytochalasin and antineoplastic agents can be administered sequentially but do not recite specific examples thereto" but cited no support for this allegation. In fact, another cited reference EP 0297946 comprises many examples. These examples, however, teach away from Applicants' invention. Example 15 discloses the simultaneous administering ADR and cytochalasin (as an association of chemotherapeutic agents) (page 12, line 11). Examples 16-18 disclose the subsequent administering of the two agents, but according to a schedule that is in contradiction to Applicants' invention: firstly, ADR is given and then, thirty or fifteen minutes later, cytochalasin is given. It is evident from this administration schedule that cytochalasin is not used as a protective agent, and could not achieve even implicitly a protective effect, for the simple reason that it is given after

ADR. In other words, Fondy et al. do not recognize the protective activity of cytochalasin but simply teach the use of cytochalasin as an antineoplastic agent. Therefore, one of ordinary skill in the art could not find in Fondy et al. any suggestion to administer cytochalasin or an equivalent compound in a (protective) pre-treatment stage of the chemotherapeutic treatment.

Furthermore, it was alleged at page 3 of the Action, "Richman et al. teach a method of treating normal and malignant cells in vitro comprising a 1 hr pretreatment of a protective compound." Actually, Richman et al. disclose only one specific "protective" compound: interferon. The pre-treatment is for only one hour (see results) and the protection is negligible, as is evident from Fig. 1. More importantly, increasing the time of exposure to interferon, and thus increasing the length of the pre-treatment, resulted in decreased survival and increased toxicity.

One of ordinary skill in the art therefore would not have combined Fondy et al. with Richman et al. for the simple reason that the former reference does not suggest that cytochalasin is a protective agent for normal cells. In other words, one of ordinary skill in the art, aware of the two cited references, would not have classified them in the same art as "protective agents" relevant to the field of Applicants' invention because the cytochalasin of Fondy et al. was neither taught nor suggested to have such activity and the interferon of Richman et al. was ineffective.

Furthermore, the Examiner maintains at page 4, last paragraph, of the Action that although neither Fondy et al. nor Richman et al. teach specific times for multiple rounds of pretreatment and treatment, "Nonetheless, one skilled in the art would find it obvious in view of routine optimization to vary the times for pretreatment and washing of the cells." But no evidence was cited or already made of record in support of this allegation. Therefore, it is nothing more than an impermissible "obvious to try" argument.

The only disclosure of pre-treatment, namely a short and poorly effective one hour treatment with IFN, is Richman et al. But Richman et al. also teach that if the pre-treatment is prolonged for over one hour, the protection is lost and the toxicity of the whole treatment is increasing. Clearly, it would not have been obvious to prolong the pre-treatment for more than one hour based on Richman et al.

On the other hand, Fondy et al. do not suggest the use of an agent capable of protecting the normal proliferating cells from the eradicative action of chemotherapeutic agents. Fondy et al. do not even disclose a pre-treatment with any substance capable of protecting the cell. In fact, cytochalasin (which is considered by Fondy et al. a chemotherapeutic in itself) is given after the first chemotherapeutic agent or concomitantly. In both administration schedules, cytochalasin would be completely ineffective in inhibiting the cytodieresis of normal cell in G1/G0 phase before submitting the same cells to the chemotherapeutic agent effect. In other words, by following the disclosure of Fondy et al., no protection of normal cells would have been achieved by one of ordinary skill in the art and such a person would not have been motivated by the cited references to experiment with pre-treatments of longer than one hour.

In view of Richman et al., one of ordinary skill in the art would have expected that a prolonged exposure to any protecting agent acting as IFN would result in decreased protection and increased toxicity as reported by the authors themselves. On the other hand, Fondy et al., Lane et al., and the other references of record in this application fail to describe alternative substances which are "protecting agents" for normal cells.

As to the newly cited document (i.e., *Avery's Drug Treatment*), it was stated at page 5 of the Action that this document teaches many alternative schedules for dosing a chemotherapeutic regime. Sections 2 and 3.2, and Table V, were specifically cited. But the sole section dealing with associations of active agents is section 3.2. This section illustrates three different approaches to combination chemotherapy (pages 1039-1040). The first is the biochemical approach aimed at decreasing the production and availability of a specific end-product vital for tumor cell growth and replication. This approach is not comparable to the claimed method of Applicants' invention. In any case, it was reported by Muggia et al. that "none of the successful combinations in use today have been developed purely as a result of this approach" (page 1040, left-hand column).

The second approach (i.e. the cytokinetic strategy) appears to be the closest to Applicants' invention. This approach relies, however, on a "synergistic effect" that two different chemotherapeutic agents can exert on those tumors displaying poor prolifera-

tive potential, while no protective activity on proliferating normal cells is envisaged by Muggia et al. Indeed, by using the intermittent chemotherapy protocol described (first vincristine and second methotrexate or cytarabine; see page 1040, left-hand column, last paragraph), severe damage would be expected of those normal cell compartments that Applicants' invention would protect. Accordingly, Muggia et al. recognized that "attempts at using this principle have not convincingly demonstrated that these conditions are met in the clinical situation and that selectivity for tumors ensues" (see page 1040, left-hand column, last paragraph).

The third approach is empirical. This is based on the use of drugs that are known to be individually active against the particular tumor when used alone. This therapeutic strategy is said to be the most successful in developing combination therapy. But being aimed at achieving the simple juxtaposition of the anti-tumor effects of two chemotherapeutic agents, this results in combination treatment that is conceptually very different from Applicants' invention.

It is therefore evident that, even assuming that one of ordinary skill in the art would have found in *Avery's Drug Treatment* motivation or suggestion to investigate the above strategies, that person would have done so without any reasonable expectation of success.

The Examiner also cited Table V. This table reports a six-page long list of all available antineoplastic drugs known at the time for cancer therapy, their administering schedules, and dosages. None of the indicated possibilities involves the administration schedule of the association of agents according to Applicants' invention. Therefore, one of ordinary skill in the art, faced by the aforementioned technical problem, would have found neither in this table nor in any of the other cited references any motivation or suggestion that could be successfully followed leading to the therapeutic strategy claimed by Applicants. On the contrary, it appears that Muggia et al. corroborate the patentability of Applicants' invention.

A final observation concerning the composition claims and kit claims. Claims 58-62 relate to delayed-release compositions, which the Action alleged were in themselves obvious because the common knowledge at the time would have been able to prepare

any suitable multilayer composition. But Applicants' invention is designed to release initially the protective compound and thereafter the chemotherapeutic compound. Said in other words, the claimed compositions should be recognized as a tool to put into practice the claimed method. Therefore, the patentability of the pending claims should be recognized in so far as the patentability of the method is also recognized. The same arguments apply to the kit of parts claims.

Withdrawal of the Section 103 rejection is requested because the invention as claimed would not have been obvious to one of ordinary skill in the art at the time it was made.

Conclusion

Applicants submit that the claims are in condition for allowance and earnestly solicit an early Notice to that effect. The Examiner is invited to contact the undersigned if any further information is required.

Respectfully submitted,

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